DOCKET NO.: ISIS-4288 PATENT

Application No.: 09/438,989

Office Action Dated: September 10, 2003

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-22. (Cancelled).

23. (Currently Amended) An oligomeric compound of the formula:

$$5'-(Nu_1-L_1)_n-Y-(L_2-Nu_2)_p-3'$$

wherein:

each Nu₁ and Nu₂, independently, has the formula:

$$R_{13}$$
 R_{14} R_{14}

wherein

Bx is a heterocyclic base moiety;

Lx is hydrogen, a protecting group or a substituent group;

one of R_{12} , R_{13} and R_{14} is hydroxyl, a protected hydroxyl, a covalent attachment to a solid support, a nucleoside, an oligonucleoside, a nucleotide, an oligonucleotide, a conjugate group or an optionally protected substituent group;

another of R_{12} , R_{13} and R_{14} is hydrogen, hydroxyl, a protected hydroxyl or an optionally protected substituent group;

the remaining of R_{12} , R_{13} and R_{14} , of Nu_1 , is L_1 ;

the remaining of R_{12} , R_{13} and R_{14} , of Nu_2 , is L_2 ;

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each L₁ and each L₂ is, independently, a phosphodiester, phosphorodithioate; chiral Sp phosphorothioate; phosphoramidate; thiophosphoramidate; phosphonate; methylene phosphonate; phosphotriesters; thionoalkylphosphonate; thionoalkylphosphotriester; boranophosphate; boranothiophosphate; thiodiester; thionocarbamate; siloxane; carbamate; sulfamate; morpholino sulfamide; sulfonamide; sulfide; sulfonate; N,N'-dimethylhydrazine; thioformacetal; formacetal; thioketal; ketal; amine (-NH-CH₂-CH₂-); hydroxylamine; hydroxylimine; hydrazinyl; amide (-CH₂-N(JJ)-C(O)-) and (-CH₂-C(O)-N(JJ)-); oxime (-CH₂-O-N=CH-); or alkylphosphorus (-C(JJ)₂-P(=O)(OJJ)-C(JJ)₂-C(JJ)₂-) internucleoside linkage, wherein each JJ is, independently, hydrogen or C₁ to C₁₀ alkyl wherein at least one of L₁ and L₂ is other than phosphodiester internucleoside linkage or a modified internucleoside linkage;

Y has the formula:

wherein:

each Rp is a chiral Rp phosphorothioate internucleotide linkage; and

each n, m and p is, independently, from 1 to 100; where the sum of n, m and p is from 3 to about 200;

with the proviso that at least one of R_{12} , R_{13} , R_{14} and L_x is a substituent group or at least one of L_1 and L_2 is a modified internucleoside linkage,

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wherein the oligomeric compound comprises from 5 to about 50 nucleosides.

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24. (Original) The oligomeric compound of claim 23 wherein at least one Nu₁ or at

least one Nu₂ comprises a substituent group.

25. (Original) The oligomeric compound of claim 24 wherein at least one Nu₁ and at

least one Nu₂ independently comprise a substituent group.

26. (Original) The oligomeric compound of claim 23 wherein each Nu₁ and each Nu₂

independently comprises a substituent group.

27. (Original) The oligomeric compound of claim 24 wherein said substituent group

is covalently attached to the 2', 3' or 5'-position of said Nu₁ or Nu₂.

28. (Original) The oligomeric compound of claim 27 wherein said substituent group

is covalently attached to the 2'-position of said Nu₁ or Nu₂.

29. (Original) The oligomeric compound of claim 23 wherein each of said substituent

groups is, independently, C₁-C₂₀ alkyl, C₂-C₂₀ alkenyl, C₂-C₂₀ alkynyl, C₅-C₂₀ aryl, O-alkyl, O-

alkenyl, O-alkylamino, O-alkylalkoxy, O-alkylaminoalkyl, O-alkyl imidazole, thiol,

S-alkyl, S-alkenyl, S-alkynyl, NH-alkyl, NH-alkenyl, NH-alkynyl, N-dialkyl, O-aryl, S-aryl, NH-

aryl, O-aralkyl, S-aralkyl, NH-aralkyl, N-phthalimido, halogen keto, carboxyl, nitro, nitroso,

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nitrile, trifluoromethyl, trifluoromethoxy, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, heterocycle, carbocycle, polyamine, polyamide, polyalkylene glycol, and polyether;

or each substituent group has one of formula I or II:

$$-Z_{0} = \left\{ (CH_{2})_{q1} - O \left(\begin{array}{c} R_{1} \\ I \\ N \end{array} \right)_{q2} \right\}_{q3} (CH_{2})_{q4} - J - E$$

$$= Z_{0} = Z_{1} \left(\begin{array}{c} Z_{1} \\ Z_{2} \end{array} \right)_{q5} = Z_{1} \left(\begin{array}{c} Z_{3} \\ Z_{2} \end{array} \right)_{q5} = I$$

$$= I = II$$

wherein:

 Z_0 is O, S or NH;

J is a single bond, O or C(=O);

E is C_1 - C_{10} alkyl, $N(R_1)(R_2)$, $N(R_1)(R_5)$, $N=C(R_1)(R_2)$, $N=C(R_1)(R_5)$ or has one of formula III or IV;

each R_6 , R_7 , R_8 , R_9 and R_{10} is, independently, hydrogen, $C(O)R_{11}$, substituted or unsubstituted C_1 - C_{10} alkyl, substituted or unsubstituted C_2 - C_{10} alkenyl, substituted or unsubstituted C_2 - C_{10} alkynyl, alkylsulfonyl, arylsulfonyl, a chemical functional group or a conjugate group, wherein the substituent groups are selected from hydroxyl, amino, alkoxy,

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carboxy, benzyl, phenyl, nitro, thiol, thioalkoxy, halogen, alkyl, aryl, alkenyl and alkynyl;

or optionally, R₇ and R₈, together form a phthalimido moiety with the nitrogen atom to which they are attached;

or optionally, R₉ and R₁₀, together form a phthalimido moiety with the nitrogen atom to which they are attached;

each R₁₁ is, independently, substituted or unsubstituted C₁-C₁₀ alkyl, trifluoromethyl, cyanoethyloxy, methoxy, ethoxy, t-butoxy, allyloxy, 9-fluorenylmethoxy, 2-(trimethylsilyl)ethoxy, 2,2,2-trichloroethoxy, benzyloxy, butyryl, iso-butyryl, phenyl or aryl;

R₅ is T-L,

T is a bond or a linking moiety;

L is a chemical functional group, a conjugate group or a solid support material;

each R₁ and R₂ is, independently, H, a nitrogen protecting group, substituted or unsubstituted C₁-C₁₀ alkyl, substituted or unsubstituted C₂-C₁₀ alkenyl, substituted or unsubstituted C₂-C₁₀ alkynyl, wherein said substitution is OR₃, SR₃, NH₃⁺, N(R₃)(R₄), guanidino or acyl where said acyl is an acid amide or an ester;

or R₁ and R₂, together, are a nitrogen protecting group or are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

or R₁, T and L, together, are a chemical functional group;

each R_3 and R_4 is, independently, H, C_1 - C_{10} alkyl, a nitrogen protecting group, or R_3 and R₄, together, are a nitrogen protecting group;

or R₃ and R₄ are joined in a ring structure that optionally includes an additional heteroatom selected from N and O;

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 Z_4 is OX, SX, or $N(X)_2$;

each X is, independently, H, C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, $C(=NH)N(H)R_5$, $C(=O)N(H)R_5$ or $OC(=O)N(H)R_5$;

 R_5 is H or C_1 - C_8 alkyl;

 Z_1 , Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic;

 Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(R_1)(R_2)$ OR_1 , halo, SR_1 or CN;

each q_1 is, independently, an integer from 1 to 10;

each q_2 is, independently, 0 or 1;

 q_3 is 0 or an integer from 1 to 10;

 q_4 is an integer from 1 to 10;

q₅ is from 0, 1 or 2; and

provided that when q_3 is 0, q_4 is greater than 1.

30-34. (Canceled).

35. (Original) The oligomeric compound of claim 23 wherein at least one R_{14} is L_1 or L_2 .

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- 36. (Original) The oligomeric compound of claim 23 wherein at least one R_{14} is L_1 and at least one R_{14} is L_2 .
 - 37. (Canceled).
- 38. (Original) The oligomeric compound of claim 23 comprising from 8 to about 30 nucleosides.
- 39. (Original) The oligomeric compound of claim 23 comprising from 15 to about 25 nucleosides.
 - 40 44. (Canceled).